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Alcohol use disorder and cannabis use disorder symptomatology in adolescents are differentially related to dysfunction in brain regions supporting face processing

Emily K. Leiker[a], Harma Meffert[b], Laura C. Thornton[b], Brittany K. Taylor[c], Joseph Aloi[b,d], Heba Abdel-Rahim[b], Niraj Shah[b], Patrick M. Tyler[b], Stuart F. White[b], Karina S. Blair[b], Francesca Filbey[e], Kayla Pope[b,f,g], Matthew Dobbertin[b], R. James R. Blair[b,*]

[a] Department of Psychiatry, Dell Medical School, University of Texas at Austin, Austin, TX, USA
[b] Center for Neurobehavioral Research, Boys Town National Research Hospital, 14100 Crawford St, Boys Town, NE 68010, USA
[c] Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE, USA
[d] Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA
[e] Center for BrainHealth, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX, USA
[f] Department of Psychiatry, University of Nebraska Medical Center, Omaha, NE, USA
[g] Department of Psychiatry, Creighton University, Omaha, NE, USA

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ABSTRACT

Despite extensive behavioral evidence of impairments in face processing and expression recognition in adults with alcohol or cannabis use disorders (AUD/CUD), neuroimaging findings have been inconsistent. Moreover, relatively little work has examined the relationship of AUD or CUD symptoms with face or expression processing within adolescents. Given the high prevalence of alcohol and cannabis use during adolescence, understanding how these usage behaviors interact with neural mechanisms supporting face and expression processing could have important implications for youth social and emotional functioning. In this study, adolescents ($N = 104$) responded to morphed fearful and happy expressions during fMRI and their level of AUD and/or CUD symptoms were related to the BOLD response data. We found that AUD and CUD symptom severity were both negatively related to responses to faces *generally*. However, whereas this relationship was shown for AUD within ventromedial prefrontal cortex and lingual gyrus, it was shown for CUD within rostromedial prefrontal cortex including anterior cingulate cortex. Additionally, AUD symptom levels were associated with differential responses within medial temporal pole and inferior parietal lobule as a function of expression. These results have potential implications for understanding the social and emotional functioning of adolescents with AUD and CUD symptoms.

1. Introduction

Adolescence is a time of rapid change in brain development (particularly in networks important for social and emotional functioning; Kilford et al., 2016) and is associated with an increased propensity for risk-taking behaviors including substance use (Casey and Jones, 2010; Cservenka and Brumback, 2017). Alcohol and cannabis use are highly prevalent during adolescence (Johnston et al., 2018; SAMHSA, 2017) and greater use during adolescence predicts a number of adverse cognitive, social, and emotional outcomes (Cservenka and Brumback, 2017; Fluharty et al., 2018; SAMHSA, 2017). Given the complexity of the social and emotional territory adolescents must learn to navigate during this time (Casey and Jones, 2010; Kilford et al., 2016) and the immense neurodevelopmental changes taking place (Kilford et al., 2016), substance use during adolescence has the potential to interfere with normative social and emotional neurodevelopmental processes (Cservenka and Brumback, 2017; Fluharty et al., 2018).

Multiple studies have linked substance use to impaired socioemotional function in adulthood (e.g., Fluharty et al., 2018; Zimmermann et al., 2017), but few have examined the relationship in adolescents. One socioemotional function that seems particularly disrupted in adults by both alcohol and cannabis dependence is face processing, particularly of emotional expressions (Castellano et al., 2015; Miller et al., 2015). Face and expression processing undergo

* Corresponding author.
E-mail address: James.Blair@boystown.org (R. .R. Blair).

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considerable neurodevelopment from adolescence to adulthood (Wu et al., 2016). Faces play an important communicatory role in everyday social interactions, conveying information about an individual's internal state and intentions so that the perceiver may understand and adapt to the social situation appropriately (Blair, 2003). As such, impairments in this processing have been linked to interpersonal difficulties in adults with alcohol dependence (Kornreich et al., 2002).

Studies of adults with alcohol use disorder (AUD) relatively consistently report impaired expression recognition relative to comparison individuals (Donadon and Osório, 2017; Foisy et al., 2007; Kornreich et al., 2002; Maurage et al., 2008) – although there are conflicting results (Dethier et al., 2014; Kornreich et al., 2016). Analogous studies in adults with cannabis use disorder (CUD) are less common, although a similar impairment is reported (Bayrakçi et al., 2015; Hindocha et al., 2014). There have been claims that these impairments reflect deficits in expression processing rather than face processing more generally (Hindocha et al., 2014; O'Daly et al., 2012; but see Kornreich et al., 2016 for an alternative view), as impairments are not seen for age or sex evaluations (Foisy et al., 2007) or identity matching tasks (Maurage et al., 2008).

Neuroimaging studies of face expression processing in patients with AUD are both fewer in number and less conclusive in results. Alcohol dependence in adults has been associated with generally reduced BOLD responses to emotional expressions in prefrontal (e.g., dorsolateral and orbitofrontal cortex), limbic (amygdala, hippocampus, insula and cingulate cortex) and other regions (e.g., parietal cortex, putamen and caudate; Alba-Ferrara et al., 2016; Marinkovic et al., 2009; O'Daly et al., 2012; Salloum et al., 2007). However, it should be noted that the reported effects and brain regions seldom replicate across studies, potentially reflecting patient population differences, task or other design discrepancies, or sample size limitations. For example, studies have used different tasks (i.e., incidental, implicit, or explicit processing tasks), emotional expressions, and selection criteria for patient and control samples (e.g., length of abstinence, whether other substance use or psychiatric history are exclusory, etc.). Moreover, even within these studies, at least one contrast has often indicated some regions showing *increased* BOLD responses, even if other contrasts in the same study indicate *decreased* BOLD responses, to emotional faces (Alba-Ferrara et al., 2016; Salloum et al., 2007). In addition, it is unclear whether the observed effects reflect reduced BOLD responses to emotional expressions or faces more generally. Some studies have considered the results to reflect reduced responses to *expressions* (O'Daly et al., 2012; Salloum et al., 2007), but the lack of neutral expressions in their experimental designs preclude the separation of general face effects from emotional face effects. Other studies have indicated reduced BOLD responses to faces generally by documenting only significant group and not group-by-expression interaction results (Alba-Ferrara et al., 2016).

The situation is similar with respect to CUD, though with fewer studies. One study reported that adults who were heavy marijuana smokers relative to non-smoking controls showed decreased BOLD responses in mid anterior cingulate cortex (ACC) and amygdala to masked angry and happy expressions, but increased responses in posterior cingulate cortex (Gruber et al., 2009). Another study reported increased amygdala BOLD responses to angry versus neutral expressions in cannabis-experimenting adolescent participants, and an undifferentiated response to angry versus neutral expressions within right middle temporal gyrus and bilateral inferior frontal gyrus (Spechler et al., 2015). However, the interpretation of the latter study is difficult as the majority of cannabis-experimenting participants (49/70) endorsed only using marijuana once or twice previously in their lives.

Two features of the previous neuroimaging work should be noted: First, most of this work was conducted with adult participants. Yet, the neurocognitive functions supporting facial and emotional expression processing continue maturing during adolescence (Kilford et al., 2016; Scherf et al., 2012; Wu et al., 2016). As such, it would be inappropriate to generalize the results of adult studies to adolescents. If adolescent substance use leads to impairments in these still-developing processes, the results could be detrimental to long-term social and emotional functioning (Casey and Jones, 2010; Scherf et al., 2012). To the authors' knowledge, there are currently no fMRI studies examining face processing related to adolescent alcohol abuse; however, there are at least two reports of altered neural responses to faces in youth with high familial risk for alcohol and other substance use disorders (Hulvershorn et al., 2013; Peraza et al., 2015). These studies reported greater activation in prefrontal and occipital regions to faces versus shapes (Hulvershorn et al., 2013), and in superior parietal lobule to neutral masked faces versus baseline fixation (Peraza et al., 2015) in youth with high familial risk relative to comparison youth. With respect to cannabis use, the evidence is even more limited (see above; Spechler et al., 2015).

Second, most prior work has contrasted neurotypical comparison individuals with individuals presenting with alcohol dependence or another substance use disorder (Alba-Ferrara et al., 2016; Gruber et al., 2009; Marinkovic et al., 2009; O'Daly et al., 2012; Salloum et al., 2007). Studies have not typically looked at the relationship between severity of AUD and CUD symptoms and level of pathophysiology. Moreover, studies have typically excluded participants with polysubstance use. Yet, in adolescents in particular, alcohol/cannabis use without significant use of the other substance is rare (Johnston et al., 2018; SAMHSA, 2017). It is unclear whether these two substances have similar or differential impacts on neural functioning. Indeed, it is possible that severity of AUD and CUD symptoms may show interactive associations with respect to neurodevelopment (e.g., see Schweinsburg et al., 2011).

To address these concerns with the previous literature, we implemented a morphed faces task (adapted from Blair et al., 2008) in a sample of adolescents with varying degrees of AUD and CUD symptomatology. Participants indicated whether faces depicting neutral expressions or fearful or happy expressions of varying intensities were male or female. Based on the previous literature, we hypothesized an inverse relationship between AUD symptom severity and BOLD responses to face stimuli within prefrontal, parietal, limbic, and inferior occipital regions, irrespective of expression displayed. Given the lack of previous literature regarding CUD and the neural systems mediating expression processing, we hypothesized only that if CUD is associated with heightened threat sensitivity, as has been suggested (Spechler et al., 2015), then increasing CUD symptomatology will be associated with increased BOLD responses within the amygdala, anterior insula and anterior cingulate cortices to fearful versus neutral expressions. We made no other expression-specific predictions, given reviews of the emotional expression literature implying relatively similar neural responses to happy and fearful expressions (Fusar-Poli et al., 2009).

2. Methods

2.1. Participants

The initial sample included 123 adolescents (77 males) aged 14–18 years, obtained from a larger ongoing fMRI study of youth recruited from a midwestern residential youth care program and surrounding community (for further details see Supplementary Section S2.1). The youth care program serves youth with behavioral and emotional problems, addressing substance abuse (at least 40% of the population) and mental health concerns (ADHD, CD, MDD and anxiety). In the interest of assessing a continuum of AUD and CUD symptomatology, youth from the surrounding community were recruited to provide a healthy "anchor point" from which to understand the impact of increasing AUD/CUD severity (similar to a patient vs. healthy comparison group design) – although some of these community participants did report psychopathology (see Table S1). Exclusion criteria for this larger study included pervasive developmental disorder, Tourette's syndrome, lifetime

Table 1
Descriptive statistics on demographic and clinical variables in the final sample of 104 youths.

Basic demographics	M	SD	Min.	Max.	Skew (S.E.)	Kurtosis (S.E.)
Age	15.95	1.23	14	18	.03 (0.24)	−0.90 (0.47)
IQ	103.78	12.78	79	135	.30 (0.24)	−0.11 (0.47)
Sex	66 male / 38 female					
Assessment scores[a]						
AUDIT total raw scores[b]	2.50	4.86	0	26	2.74 (0.24)	8.21 (0.47)
CUDIT total raw scores[b]	5.48	8.49	0	32	1.45 (0.24)	1.03 (0.47)
Rankit transformed Z-scored AUDIT total scores	0	1	−0.76	1.95	.70 (0.24)	−1.27 (0.47)
Rankit transformed Z-scored CUDIT total scores	0	1	−0.80	1.89	.62 (0.24)	−1.35 (0.47)
Cigarette smoking[c]	1.02	1.39	0	4	.91 (0.24)	−0.70 (0.47)
CBCL externalizing total raw score	17.86	15.78	0	52	.53 (0.25)	−1.01 (0.47)
SCARED total raw score	19.91	15.09	0	57	.83 (0.24)	−0.29 (0.47)
MFQ total raw score	11.41	12.00	0	54	1.74 (0.25)	3.05 (0.47)
Psychiatric diagnoses[d]	% of sample					
ADHD	49.04					
CD	37.50					
MDD	17.31					
GAD	25.00					

Note:.
[a] Cigarette smoking, CBCL, SCARED, and MFQ scores are missing for some participants, as these assessments were optional (resulting n = 101, 91, 102, and 95, respectively).
[b] AUDIT and CUDIT Total Raw Scores were not used in any analyses, but are presented here to demonstrate the excessive skew and kurtosis which were reduced by Rankit transformation and z-scoring.
[c] Cigarette smoking was coded as 0 = "Never", 1 = "Once or twice", 2 = "Occasionally, not regularly", 3 = "Regularly in the past", and 4 = "Regularly now".
[d] Diagnostic information on internalizing disorders was incomplete for two participants due to incomplete psychiatric interviews; CD = Conduct Disorder, ADHD = Attentional Deficit Hyperactivity Disorder, MDD = Major Depressive Disorder, GAD = Generalized Anxiety Disorder.

history of psychosis, neurological disorders, head trauma, pregnancy, presence of metallic objects in the body (e.g., metal plates, pacemakers, etc.), any non-psychiatric medical illness requiring the use of medications with potential psychotropic effects (e.g., beta-blockers or steroids), and an IQ below 75 (as assessed with the Wechsler Abbreviated Scale of Intelligence, WASI-II; Wechsler and Zhou, 2011). With respect to the identified sample, 19 participants were excluded prior to analysis due to excessive movement (average motion per TR > the group mean plus two SDs; n = 4), poor behavioral response rate (missed responses in the conditions of interest > two SDs above the group mean, n = 9), or suspected artifacts/image processing failures that could not be corrected (e.g., realignment non-convergence; n = 6). Participant exclusion was not associated with AUD symptomatology or CUD symptomatology (rs = −0.09 and −0.12, ps = 0.34 and 0.19). This resulted in a final sample of 104 youth (67 from the residential program); average age = 15.95 years (SD = 1.23; range 14–18), IQ = 103.78 (SD = 12.78) and 66 males (see Table 1).

Clinical symptomatology was characterized through psychiatric interviews conducted with the youth and their parents/legal guardians by a licensed psychiatrist, in close adherence to common clinical practice. Most participants with significant substance abuse histories (i.e., those scoring above cutoffs on the substance use assessments, detailed below) were residents of the residential program and were abstinent for at least four weeks prior to scanning. Written informed assent/consent was obtained from all participants and their parent or legal guardian by a doctoral level researcher or clinician prior to the study, in accordance with the study procedures approved by the Institutional Review Board. Participation was voluntary and all participants were financially compensated for their participation ($50 per scan visit).

2.2. Measures

2.2.1. Substance use assessments

To characterize AUD and CUD symptoms within our sample, the youths completed the Alcohol Use Disorder Identification Test (AUDIT) and Cannabis Use Disorder Identification Test (CUDIT; Adamson et al., 2010; Fairlie et al., 2006; Saunders et al., 1993). These scales assess overall alcohol and cannabis consumption and symptoms of alcohol and cannabis abuse or dependence *over the past year*. Both scales demonstrate high external validity, as evidenced by the predictive relationship between clinical cutoff scores on these assessments (≥4 AUDIT; ≥8 CUDIT) and diagnoses in both adult (Adamson et al., 2010; Saunders et al., 1993) and adolescent populations (Annaheim et al., 2008; Fairlie et al., 2006). Note that drug tests are also irregularly administered to the participants in the residential care program as part of their care. Cigarette smoking was determined with an item from the Monitoring the Future Survey (Miech et al., 2018) assessing past and current cigarette smoking behavior. Additional information on these assessments is provided in the Supplemental Materials.

2.2.2. Psychiatric symptomatology assessments

To characterize psychiatric comorbidities within our sample, assessments of externalizing, anxious, and depressive symptomatology were administered to participants and their parents. Parents completed the externalizing problems subscale of the parent-report version of the Childhood Behavior Checklist (CBCL) to characterize externalizing behaviors of the participants (Achenbach and Rescorla, 2001). The youths completed the child self-report versions of the Screen for Child Anxiety and Related Disorders (SCARED) and the Mood and Feelings Questionnaire (MFQ; long version) to assess levels of anxiety and depressive symptoms, respectively (Angold et al., 1995; Birmaher et al., 1997).

2.2.3. Faces task

fMRI was acquired while participants completed an expression processing task adapted from an earlier version (Blair et al., 2008). In this task, participants indicated whether a face was male or female for a series of photographs of faces of 10 men and women displaying either neutral or intensity morphed (50, 100, or 150%) happy or fearful expressions (depicted in Figure S1; see Supplemental Materials for more information on stimuli creation). Each trial consisted of a face presented for 2000 ms, followed by a jittered fixation cross for 500–3000 ms. Participants were instructed to indicate the sex of each face with a left-right button press using the index and middle finger of their right hand during a single run (~9.5 min) of 160 trials (60 Fear, 60 Happy, 40 Neutral).

2.3. Imaging procedures and preprocessing

2.3.1. Image acquisition

Whole-brain blood oxygen level dependent (BOLD) data was acquired using a 3.0 Tesla Siemens Skyra Magnetic Resonance Scanner. A total of 236 functional images were acquired over a single run, using a T2* weighted gradient echo planar imaging (EPI) sequence (TR = 2500 ms, TE = 27 ms; 94 × 94 matrix; 90° flip angle; 240 mm field of view) with 43 axial slices (2.5 mm thickness, 0.5 mm spacing; voxel size 2.6 × 2.6 × 2.5 mm^3). A high-resolution T1 anatomical scan (MP-RAGE; TR = 2200 ms, TE = 2.48 ms; 230 mm field of view; 8° flip angle; 256 × 208 matrix) with 176 axial slices (1 mm thickness, voxel size 0.9 × 0.9 × 1 mm^3) was acquired in the same session to register with the EPI dataset.

2.3.2. Preprocessing

All fMRI data were preprocessed and analyzed in Analysis of Functional Neuroimages (AFNI; Cox, 1996). Data from the first four TRs prior to magnetization equilibrium were not collected. Functional images were despiked and slice-time corrected. The anatomical scan for each participant was registered to the minimal outlier volume of their functional images, then registered to the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) using the TT_N27 template. Functional images for each participant were motion corrected by registering all volumes from the EPI dataset to the minimal outlier volume, then warped to Talairach space and spatially smoothed with a 6 mm full width half maximum Gaussian kernel, before undergoing time series normalization. For normalization, the signal intensity of each voxel at each time-point was divided by the mean signal intensity of that voxel for each run, then multiplied by 100 for each voxel so that the resulting regression coefficients represent a percentage of signal change from the mean.

2.4. Statistical analyses performed

To reduce skewness and kurtosis, the AUDIT and CUDIT total scores were first Rankit transformed (Soloman and Sawilowsky, 2009), then z-scored to place both on the same scaling prior to analysis (see Table 1).

2.4.1. Clinical correlations

Zero-order correlation analyses were conducted to assess the associations of the transformed, z-scored AUDIT and CUDIT scores with cigarette smoking, age, IQ, sex, externalizing score on the CBCL, SCARED and MFQ total scores, and whether the individual received a particular diagnosis or not (scored 1 or 0 respectively). To evaluate whether AUDIT and CUDIT scores differentially correlated with these variables, *Steiger's Z*-tests were conducted on the zero-order correlations using freely available online tools (Lee and Preacher, 2013). For all of these analyses significance was considered at $p < .05$.

2.4.2. fMRI analysis

2.4.2.1. Individual-level (within-subjects) analysis. Individual-level whole brain functional data was modelled via linear regression using six indicator regressors (Fear, Happy, Neutral, LowFear, LowHappy, and Misses), plus six regressors modeling motion and four regressors modeling a cubic polynomial baseline drift function. The regressors of interest were Fear, Happy, and Neutral, based on the stimulus onsets for moderate (100%) to high (150%) intensity fearful and happy expressions, and 0% intensity expressions, respectively. Regressors were also generated for stimulus onsets from the low (50%) intensity fearful and happy expression conditions (LowFear and LowHappy, respectively) and for stimulus onsets associated with missed responses (Missed); but these were not of interest and were not included in the second-level analysis. All regressors were created by convolving the train of stimulus events with a gamma variate hemodynamic response function, to account for the slow hemodynamic response. TRs with motion exceeding 0.2 mm were censored along with the preceding TR. The resulting output included a beta coefficient and associated t-statistic for each voxel and regressor.

2.4.2.2. Second-level (between subjects) analysis. A repeated measures ANCOVA was performed on the second-level BOLD data within a gray matter mask created in AFNI, with a three-level within subject factor of Expression (Fear, Happy, Neutral), including AUDIT and CUDIT scores, sex, age, and full interaction terms as covariates. Age was included as a nuisance covariate in the model due to the significant associations between AUDIT and CUDIT scores and age in the current sample. Sex was also included as a covariate to determine whether the effects of AUDIT and CUDIT scores generalized across sex in the current sample.

Correction for multiple comparisons was performed using a spatial clustering operation in AFNI's 3dClustSim utilizing the autocorrelation function (-acf) with 10,000 Monte Carlo simulations for the whole-brain analysis. The initial uncorrected threshold was set at $p < .001$ (Cox et al., 2017a, 2017b). This process yielded an extent threshold of $k = 24$ voxels at a family wise error rate of $p < .05$. Post-hoc analyses were conducted on the average percent signal change within all significant clusters to examine significant main effects and interactions, with planned follow-up testing implemented in SPSS 22.0 (IBM SPSS Statistics for MacOSX, 2012). Key significant effects were characterized by calculating the partial correlations (ρ) between AUDIT or CUDIT scores and corresponding BOLD responses, controlling for all other covariates and interaction terms.

3. Results

3.1. Clinical data

Of the 104 participants, 51 (49%) endorsed at least some AUD/CUD symptoms (AUDIT/CUDIT score >0) in the past year. Across the sample, AUDIT scores ranged from 0 to 26 ($M = 2.5$; SD = 4.9) and CUDIT scores from 0–32 ($M = 5.5$; SD = 8.5).

Of the 51 youths who endorsed past year alcohol and/or cannabis use, 36 met the cutoffs on either the AUDIT (AUDIT ≥4; Fairlie et al., 2006) or the CUDIT (CUDIT ≥8; Adamson et al., 2010). Consistent with prior reports of high rates of poly-substance use in adolescents (Gray and Squeglia, 2018; Mason et al., 2013; Moss et al., 2014), 17 of these youth met the cutoffs for both AUD and CUD; whereas 7 met the cutoff for AUD only and 12 for CUD only. Both AUDIT and CUDIT scores correlated positively with age ($rs = 0.26$ and 0.21, $ps = 0.01$ and 0.04), but there were no significant relationships of AUDIT and CUDIT scores with sex or IQ ($rs = -0.17$ to 0.16, $ps = 0.09$ to 0.82; see Table 2). Additionally, AUDIT and CUDIT scores were unrelated to measures of behavioral performance or motion ($rs = -0.18$ to 0.12, $ps = 0.07$ to 0.98; see Table S2).

Zero-order correlation analyses were conducted to examine the relationships of AUDIT and CUDIT scores with other psychiatric symptomatology and cigarette smoking (see Table 2). These revealed significant positive correlations between AUDIT and CUDIT scores ($r = 0.65$, $p < .001$), and between both and cigarette smoking ($rs = 0.67$ and 0.65, $ps < 0.001$). Additionally, AUDIT and CUDIT scores were significantly positively correlated with levels of externalizing symptoms (CBCL Externalizing Total Raw Score: $rs = 0.45$ and 0.49, $ps < 0.001$), anxiety symptoms (SCARED Total Raw Score: $rs = 0.20$ and 0.22, $p = .046$ and 0.03 respectively), but only CUDIT scores were significantly positively correlated with depression symptoms (MFQ Total Raw Score: $r = 0.22$, $p = .03$; whereas $r = 0.18$, $p = .09$ for AUDIT). Importantly, there were no significant differential correlations between AUDIT and CUDIT scores for any of the above psychiatric measures or cigarette smoking (*Steiger's Zs* = −0.51 to 0.34, $ps = 0.60$ to 0.81).

Table 2
Zero-order Pearson's correlation coefficients (*r*) across demographic and clinical variables in 104 youths (*p*-values in parentheses).

	1	2	3	4	5	6	7	8	9
1. Age	–								
2. Sex[a]	−0.13 (0.18)	–							
3. IQ	.11 (0.27)	−0.03 (0.76)	–						
4. Rankit transformed Z-scored AUDIT total scores	**.26*** (0.007)	.15 (0.14)	−0.17 (0.09)	–					
5. Rankit transformed Z-scored CUDIT total scores	**.21** (0.036)	−0.02 (0.82)	−0.16 (0.10)	**.65**† (<0.001)	–				
6. Cigarette smoking[b,c]	**.23** (0.019)	−0.04 (0.69)	−0.14 (0.17)	**.67**† (<0.001)	**.65**† (<0.001)	–			
7. Externalizing behavior[b,d]	.10 (0.34)	−0.08 (0.46)	**−0.22** (0.039)	**.45**† (<0.001)	**.49**† (<0.001)	**.52**† (<0.001)	–		
8. Anxiety symptoms[b,d]	.05 (0.62)	**.26*** (0.009)	.10 (0.34)	**.20** (0.046)	**.22** (0.030)	**.20** (0.045)	.17 (0.11)	–	
9. Depression symptoms[b,d]	.03 (0.79)	**.23** (0.028)	−0.01 (0.96)	.18 (0.09)	**.22** (0.034)	.19 (0.08)	.15 (0.17)	**.70**† (<0.001)	–

Note:.
[a] Sex was coded as 0 = Male, 1 = Female.
[b] Cigarette smoking, CBCL, SCARED, and MFQ scores are missing for some participants, as these assessments were optional (n = 101, 91, 102, and 95, respectively).
[c] Cigarette smoking was coded as 0 = "Never", 1 = "Once or twice", 2 = "Occasionally, not regularly", 3 = "Regularly in the past", and 4 = "Regularly now".
[d] Externalizing Behavior is the CBCL Externalizing Subscale Total Raw Score, Anxiety Symptoms are the SCARED Total Raw Score, and Depression Symptoms are the MFQ Total Raw Score; significant correlations at $p < .05$ are bolded (*p*-values in parentheses).
* Indicates correlations significant at $p < .01$.
† Indicates correlations significant at $p < .001$.

3.2. Behavioral results

Two three-level (Expression: Fear, Happy, Neutral) repeated measures ANCOVAs were conducted on the average accuracy and response time (RT) data, including AUDIT and CUDIT scores, age, sex, and full interaction terms as covariates. This analysis revealed no significant results for average accuracy or RT (Fs = 0.03–2.77, ps = 0.07–0.97).

3.3. fMRI results

The main aim of the present study was to evaluate whether neural responses to an expression processing task varied according to AUD and CUD symptomatology in adolescents. To that end, we conducted a repeated measures ANCOVA with one within subjects factor (Expression: Fear, Happy, Neutral), including covariates for AUDIT and CUDIT scores, age, sex, and full interaction terms. With respect to our hypotheses, this revealed regions displaying main effects of both AUD and CUD symptoms and regions showing an AUD Symptoms-by-Expression interaction (reported in Table 3). The corresponding partial correlation coefficients for these key significant effects and interactions are provided in Table S3. All other significant results, including a main effect of emotion and interactions involving age and sex, are reported in Table S4.

3.3.1. Main effect of AUD symptoms

A main effect of AUD symptoms was seen within both left ventromedial prefrontal cortex (vmPFC) and left lingual gyrus (LG; see Fig. 1A and B). Within both regions, there were significant negative associations between AUDIT scores and BOLD responses to face stimuli (rs = −0.47 and −0.43; ps < 0.001).

3.3.2. Main effect of CUD symptoms

A main effect of CUD symptoms was seen within left rostromedial prefrontal cortex (rmPFC; see Fig. 1C and D), including left caudal ACC. Within this region, there was a significant negative association between CUDIT scores and BOLD responses to face stimuli (r = −0.44, p < .001).

3.3.3. AUD symptoms x expression interaction

There was a significant interaction between AUD symptoms and Expression in right medial temporal pole (MTP) and left inferior parietal lobule (IPL; see Fig. 2). To characterize the interaction, we calculated the partial correlations between AUDIT scores and the differential BOLD responses for Fear > Neutral and Happy > Neutral expressions in each region, controlling for CUD symptoms, age, sex, and all other interaction terms. AUDIT scores were significantly positively correlated with differential BOLD responses in MTP to Fear > Neutral expressions (ρ = 0.39, p < .001) and Happy > Neutral expressions (ρ = 0.35, p = .001), and significantly negatively correlated with differential BOLD response in IPL to Fear > Neutral faces (ρ = −0.40, p < .001). The partial correlations between AUDIT scores and BOLD responses to each expression are provided in Table S3.

3.3.4. Follow-up analyses

To evaluate the consistency of our findings with traditional group-based analyses, we conducted comparable follow-up repeated measures ANOVAs including one within subjects factor (Expression: Fear, Happy, Neutral) and one between subjects group factor based on either AUD symptoms (adolescents with AUDIT scores ≥4, n = 23; and an age, IQ, sex matched comparison group with AUDIT scores = 0, n = 26) or CUD symptoms (adolescents with CUDIT scores ≥8, n = 29; and an age, IQ, sex matched comparison group with CUDIT scores = 0, n = 29). These matched comparison groups were drawn from the 53 participants who did not endorse alcohol or cannabis use. Participant characteristics for these group analyses are provided in Tables S5 and 6.

The follow-up group analysis for CUD symptoms showed a main

Table 3
Brain regions demonstrating key significant effects and interactions of AUD and/or CUD symptoms from an analysis of covariance on BOLD response to faces > baseline fixation during a face expression task in 104 youths (multiple comparison corrected to *p*FWE < 0.05).

Region[a]	Coordinates of Peak Activation[b]							
	Voxels	BA	x	y	z	$F^{\dagger}$	β	$H^{b}_{partial}$
Main Effect of AUD Symptoms								
L. rostral middle frontal cortex/superior orbital gyrus	44	10	−19	54	4	27.61	−0.041	0.05
L. lingual gyrus/calcarine gyrus	27	18	−4	−94	−6	22.08	.491	0.09
Main Effect of CUD Symptoms								
L. superior medial frontal cortex/anterior cingulate cortex	57	9	−1	36	34	20.07	−0.057	0.16
AUD Symptoms x Expression Interaction								
R. medial temporal pole/uncus/fusiform gyrus	46	36	24	1	−31	18.57	.043	0.02
L. inferior parietal lobule/supramarginal gyrus	31	40	−56	−41	44	12.39	.003	0.07

Note:
[a] According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/).
[b] Based on the Tournoux & Talairach standard brain template; BA = Brodmann's Area, $\eta^{2}_{partial}$ = partial eta squared effect size estimate, β = average percent signal change from the mean.
† *p*FWE < 0.05 (voxelwise *p* < .001, uncorrected; *k* = 24 voxels).

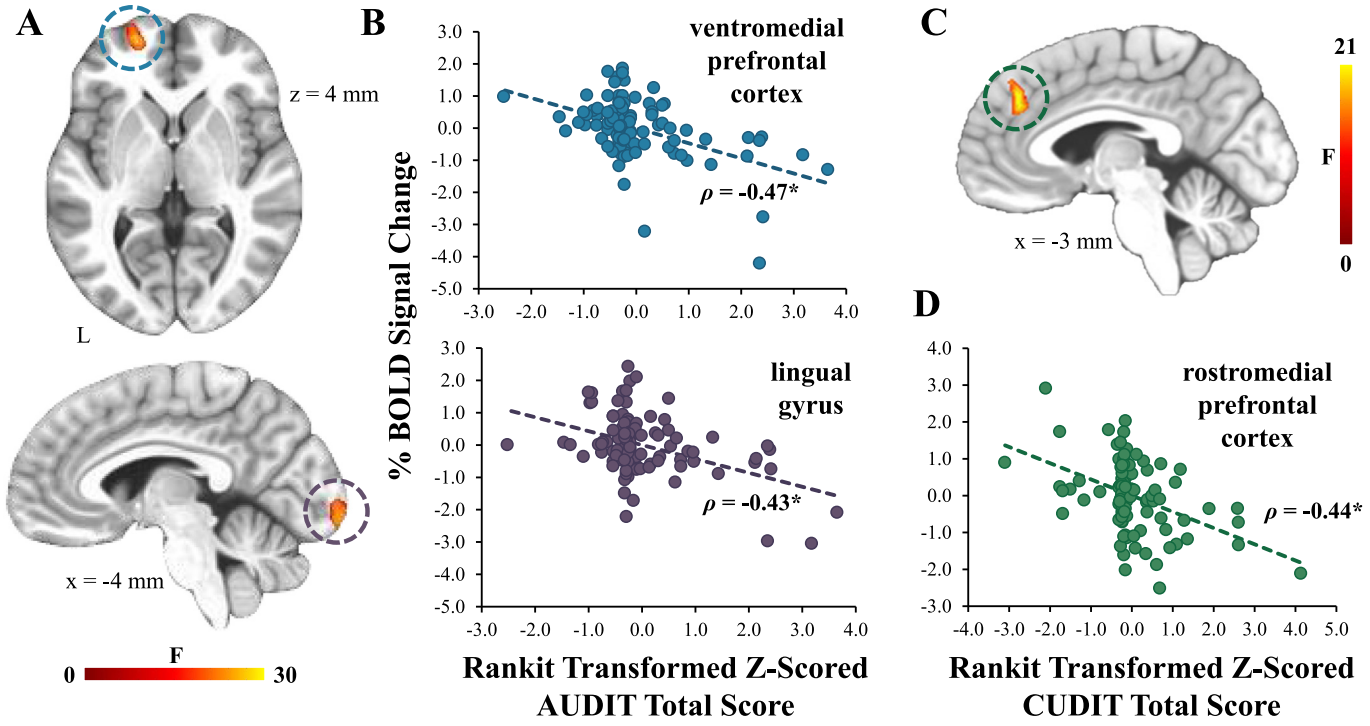

Fig. 1. Regions showing significant effects of AUD and CUD symptoms on BOLD response to faces. (A) Clusters within vmPFC and LG showing significant main effects of AUD symptoms on BOLD response to faces. (B) BOLD responses in these regions were significantly negatively correlated with AUDIT scores. (C) A cluster within rmPFC showing a significant main effect of CUD symptoms on BOLD response to faces. (D) BOLD response in this region was significantly negatively correlated with CUDIT scores. Plots depict partial correlations and adjusted residuals for each region, with dotted lines depicting the corresponding partial correlation coefficients (ρ). *L* = left hemisphere. *indicates partial correlations significant at *p* < .001.

effect of Group in right rmPFC/ACC (peak voxel: $x = 4, y = 36, z = 34$; 25 voxels), proximal to the left rmPFC/ACC region identified in the ANCOVA analysis, albeit at a more lenient threshold ($p < .005$, uncorrected). The comparable group analysis for AUD symptoms showed a main effect of Group in left vmPFC (peak voxel: $x = 21, y = 54, z = 4$; 6 voxels) and a Group-by-Expression interaction in left IPL (peak voxel: $x = 54, y = -31, z = 41$; 12 voxels), both overlapping with the regions identified in the ANCOVA analysis, albeit at a more lenient threshold ($p < .005$, uncorrected). No other effects from the main ANCOVA analysis emerged at this threshold.

To determine the relationship of AUDIT and CUDIT scores and BOLD responding to emotional facial stimuli in only those who had engaged in some alcohol/cannabis use (i.e., without the "anchor point" of non-using participants), we repeated our main ANCOVA following the removal of all participants with AUDIT and CUDIT scores of 0 ($n = 53$). This revealed the association of CUD symptoms and BOLD response to face stimuli within rmPFC (peak voxel: $x = -1, y = 36, z = 31$; 49 voxels) and the AUDIT-by-Expression interaction in right fusiform gyrus (peak voxel: $x = 31, y = -6, z = -36$; 127 voxels). However, the other associations with AUDIT scores were no longer significant.

3.3.5. Potential confounds

To account for the potential confounding influence of current cigarette smoking on our results, the main ANCOVA analysis was repeated with participants who endorsed current regular cigarette

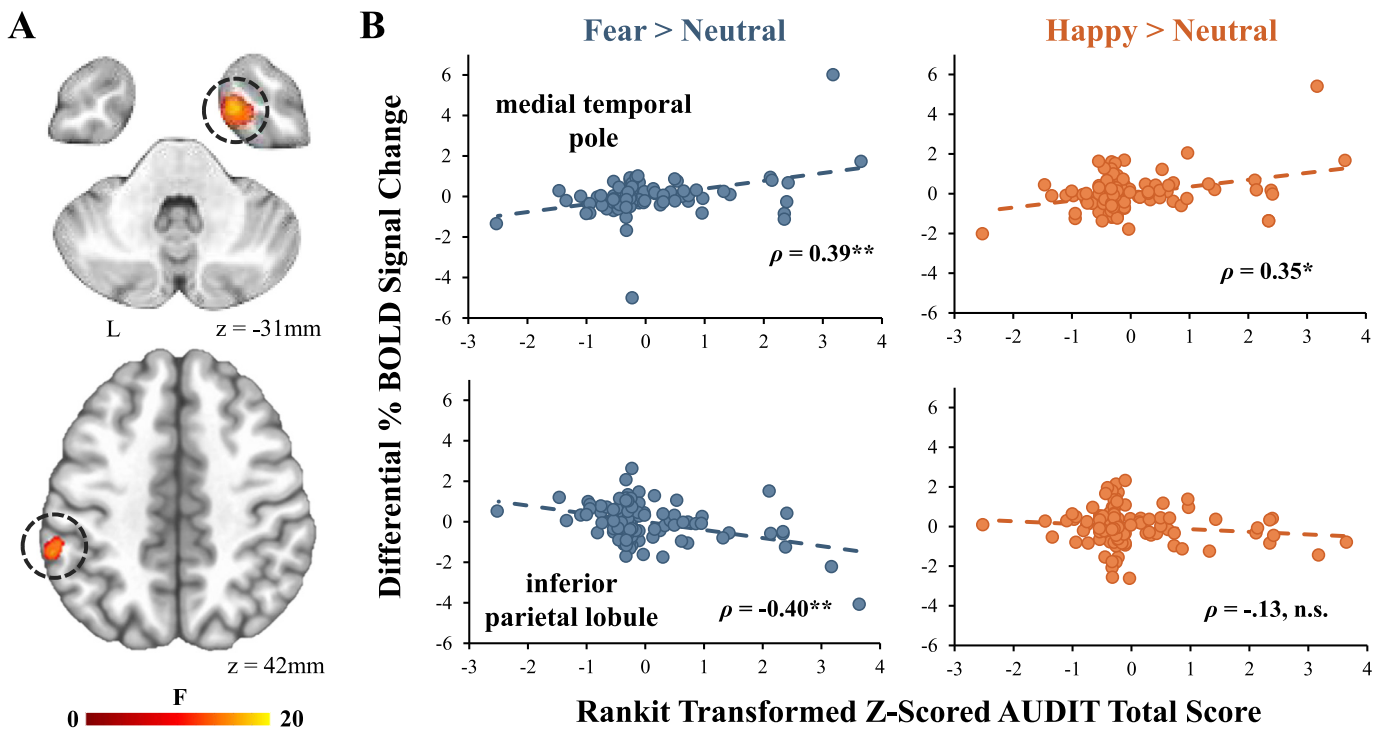

Fig. 2. Regions showing a significant AUD symptoms-by-Expression interaction. A) Clusters within MTP and IPL showing a significant interaction between AUD symptoms and expression on BOLD response to faces. (B) Plots depict partial correlations and adjusted residuals for the differential BOLD response to Fear > Neutral and Happy > Neutral expressions in these regions and AUDIT scores. Dotted lines represent the associated partial correlation coefficients (ρ). *L* = left hemisphere. **indicates partial correlation values significant at $p < .001$; *indicates partial correlation values significant at $p < .01$.

smoking excluded from the sample. This analysis showed the same effects as the main ANCOVA analysis (see Table S7), but with the left LG, rmPFC/ACC and IPL effects falling just below the minimum cluster size to survive FWE correction (22, 22 and 20 voxels, respectively; $k = 24$).

Given that drug use of community participants was less monitored than participants within the residential community, the main ANCOVA analysis was repeated with participants from the community ($n = 37$) excluded from the sample. This analysis revealed activations in the same regions as the original analysis, although only the association of CUD symptoms with activity within medial frontal cortex/anterior cingulate cortex survived correction for multiple comparisons (see Table S8).

While there were no significant differences in the associations between psychiatric diagnosis and AUDIT relative to CUDIT scores (see above), it is possible that the results above might be attributable to comorbid psychiatric pathology. We thus repeated the main ANCOVA analysis four times, adding presence/absence (coded as 1/0) covariates for the main comorbid conditions: ADHD, CD, MDD and GAD. The results of these analyses are reported in Tables S9-S12 (note only results in regions proximal to the main analysis findings are reported to reduce concerns of multiple testing). These largely revealed activations in the same regions as the original analysis (though not all results survived correction for multiple comparisons). Note that none of these analyses revealed significant associations of the comorbid condition with activity in the regions identified by the main analysis.

4. Discussion

The current study investigated the relationships between AUD and CUD symptom severity and dysfunction in neural systems supporting facial expression processing in adolescents. There were three main findings. First, in line with our predictions, we identified reduced BOLD responses to faces within prefrontal and occipital cortex as a function of increasing AUD symptom severity, irrespective of the expression displayed. Second, we observed differential relationships between AUD symptom severity and expression-specific responses within MTP and IPL. Third, in contrast to predictions, increasing CUD symptom severity was not associated with increased BOLD responses within the amygdala to fearful expressions but rather reduced BOLD responses in middle frontal cortex to faces regardless of expression displayed.

Notably, both increasing AUDIT and increasing CUDIT scores were associated with reduced BOLD responses to faces regardless of the specific facial expression displayed. For increasing AUDIT scores, this was seen within left vmPFC and left LG. For increasing CUDIT scores, this was seen within a region of left rmPFC which included ACC. Reduced responses to face stimuli in the above regions, or proximal areas, have been reported in previous work with adults with AUD (Alba-Ferrara et al., 2016; Marinkovic et al., 2009; O'Daly et al., 2012; Salloum et al., 2007) and CUD (Gruber et al., 2009). Importantly, considerable previous work has shown that these prefrontal and occipital regions respond to face stimuli (Fusar-Poli et al., 2009) and are considered part of the distributed face processing system (Haxby et al., 2000). Thus, the observed effects are consistent with the interpretation that increasing AUD and CUD severity are associated with the disrupted functioning of neural regions engaged in face processing. This is likely to lead to difficulties in social cognition and empathy and may increase the risk for aggression (Blair, 2003).

The current findings also suggest distinct patterns of neural dysfunction associated with AUD versus CUD symptomatology: whereas greater AUD symptom severity was associated with reduced face processing responses in early visual cortex (left LG) and vmPFC, greater CUD severity was related to reduced face sensitivity in a separate region of prefrontal cortex (rmPFC) which included ACC. Notably, the follow-up group comparisons based on AUD and CUD symptomatology yielded similar distinct effects in prefrontal cortex (albeit at more lenient statistical thresholds). However, given the relative absence of previous work in *adolescents* with substance abuse difficulties and lack of consistency among adult work, more work is needed to determine the

reliability of these potential distinct effects of alcohol and cannabis abuse during adolescence. Additionally, given that consistent findings emerged across both the diagnostic group and covarying analysis (ANCOVA) approaches, further investigation is needed to determine whether these effects reflect AUD or CUD symptom severity dimensionally, or if they instead emerge categorically once a particular level of AUD or CUD symptomatology is reached.

The indications of distinct patterns of neural dysfunction associated with AUD versus CUD symptomatology have implications with respect to models of substance abuse. A core model of substance abuse (Koob and Volkow, 2016) stresses the impact of the rewarding effects of the abused substances with respect to the dopamine and opioid systems and implications of this for neural function and structure. However, most substances of abuse, and certainly both alcohol and cannabis, have toxic impacts additional to the impact on the dopamine and opioid systems. Alcohol's toxic/metabolic effects on the brain are thought to be mediated by a cyclical mechanism in which oxidative stress and neuroinflammation lead to neurotoxic degeneration and impaired neurogenesis (de la Monte and Kril, 2014). For cannabis, the neurotoxic effects are thought to stem from the action of its primary psychoactive compound, tetrahydrocannabinol (THC), resulting in morphological changes in brain regions containing dense concentrations of cannabinoid receptors, including the hippocampus, amygdala, basal ganglia, and frontal cortex (Bloomfield et al., 2019). It is possible that the distinct patterns of neural dysfunction associated with AUD versus CUD symptomatology reflect differential toxic impacts of alcohol and cannabis.

Our observation of expression-specific relationships between AUD symptom severity and activation in MTP and IPL was unpredicted. The effect was driven by significant differential relationships between AUDIT scores and fearful relative to neutral expressions in both regions, and happy relative to neutral expressions in MTP. Within right MTP, increasing AUDIT scores were associated with significantly greater BOLD responses for both fearful and happy relative to neutral expressions. Within left IPL, increasing AUDIT scores were associated with significantly reduced BOLD responses for fearful relative to neutral expressions. Both of these regions are considered part of the extended face processing system (Haxby et al., 2000), and are regularly reported to show responses to facial expressions (Fusar-Poli et al., 2009; Olson et al., 2007). However, given that the follow-up group analysis showed an AUD Symptoms-by-Expression interaction within left IPL only, the above MTP finding should be interpreted cautiously. Additionally, although there is at least one report of reduced parietal activation to faces in adults with alcohol dependence (Alba-Ferrara et al., 2016), this does not appear to be expression-specific. As such, the reasons for expression-specific relationships between activation in these regions and AUD symptom severity is currently unclear and requires further study. Though the IPL result, at least, may indicate that compromised face processing as a function of AUD may be particularly severe for distress cues, such as fearful expressions, possibly resulting in empathy deficits and increasing the risk for aggression (cf. Blair, 2003).

Given the absence of behavioral effects of AUD or CUD symptom severity on response time or accuracy to faces generally or as a function of expression in the current study, the observed fMRI effects are unlikely to reflect potential visual processing deficits related to either AUD or CUD (as has been suggested for adults with chronic or severe alcohol use disorders; see D'hondt et al., 2014a, 2014b; Maurage et al., 2008). Similarly, another study (Aloi et al., 2018) with similar sample characteristics to the present study reported no behavioral or cortical fMRI effects related to AUD or CUD symptom severity for emotion condition (positive, neutral, or negative) in a task involving different classes of visual stimuli (scenes and numbers). Taken together, these results are inconsistent with the interpretation that the effects reported here reflect an underlying visual deficit related to adolescent AUD or CUD symptoms. At present, it is unclear whether this discrepancy from the adult work represents a developmental difference or merely a difference in cumulative levels of alcohol or cannabis use. Future work is needed to determine whether such a deficit would emerge longitudinally or with greater cumulative levels of consumption.

Finally, we note that our prediction of increased BOLD responses within the amygdala to fearful expressions with increasing CUD symptom severity (informed by Spechler et al., 2015) was not supported. However, given the very low rates of cannabis usage in the sample reported in that study, their finding may reflect risk rather than consequences of cannabis abuse. Indeed, prior work has indicated that youth at increased risk for substance use disorders show elevated BOLD responses to expression stimuli either within the amygdala (Elsayed et al., 2018) or cortical structures (Hulvershorn et al., 2013; Peraza et al., 2015). As such, elevated BOLD responses to expressions signaling threat may be a risk factor for substance abuse (Elsayed et al., 2018) even if, at least at the neural level, it does not emerge as a feature of substance abuse.

There are several potential limitations to the present study. First, the high degree of psychiatric comorbidity among participants with greater AUD and/or CUD symptomatology carries the risk that our findings may reflect features of the comorbid conditions, rather than AUD and CUD symptoms per se. Previous work has often either not characterized potential comorbid psychiatric conditions (Alba-Ferrara et al., 2016), characterized but not controlled for comorbid psychiatric conditions (Gruber et al., 2009; Salloum et al., 2007), or excluded participants with comorbid psychiatric conditions (Marinkovic et al., 2009; O'Daly et al., 2012). This latter strategy is potentially problematic as such participants are somewhat atypical; the vast majority of youths in treatment for AUD and/or CUD have at least one comorbid psychiatric condition (Chan et al., 2008; Couwenbergh et al., 2006). Indeed, approximately 50% of patients with AUD or other substance use disorders present with a comorbid condition (SAMHSA, 2017) and previous epidemiological work has reported that increasing AUDIT and CUDIT scores are associated with increasing psychiatric psychopathology (Kuperman et al., 2001; Moss et al., 2014; Moss and Lynch, 2001). Importantly, in the current study, there were no significant differences in the strength of the relationships between psychiatric comorbidities and AUD/CUD symptom severity. As such, the findings of differential associations of AUD/CUD symptomatology with BOLD responses to faces in the current study are difficult to interpret via reference to psychiatric comorbidities. Moreover, a series of additional ANCOVA analyses considering the main comorbid conditions present in this sample revealed similar results to the main analysis, and critically none of these analyses revealed significant associations of the comorbid condition with activity in the regions identified by the main analysis. Second, this study was cross-sectional. As such, the current findings may reflect predisposing risk factors for adolescent substance abuse or the impact of alcohol and/or cannabis abuse on the developing brain. Mitigating this concern, and as noted above, risk factors for the development of alcohol and/or cannabis abuse appear to relate to *heightened BOLD responses to emotional stimuli* (Elsayed et al., 2018; Hulvershorn et al., 2013; Peraza et al., 2015) rather than the decreased responses observed here and reported in most previous work in adults with these conditions (Alba-Ferrara et al., 2016; Gruber et al., 2009; Marinkovic et al., 2009; O'Daly et al., 2012; Salloum et al., 2007). Third, we did not conduct urine drug screens or breath alcohol testing at the time of scanning. Mitigating this concern, the participants from the residential youth care program receive random drug screens and tight monitoring. Analysis of data from only the participants from the residential youth care program revealed similar results to our main analysis.

To summarize, we identified relationships between AUD and CUD symptom severity in adolescents and reduced BOLD responses to face stimuli within brain regions supporting generalized face processing. AUD severity was associated with reduced BOLD responses to faces within vmPFC, but enhanced BOLD responses to faces within LG. CUD severity, on the other hand, was related to reduced BOLD responses to

faces within rmPFC, including a portion of ACC. Finally, we identified expression-specific effects of AUD symptom severity within IPL and MTP, which appeared to be driven by differential BOLD responsiveness to fearful versus neutral expressions in both regions and to happy versus neutral expressions in medial temporal pole. These data suggest that AUD and CUD symptom severity in adolescents is associated with differential negative impacts on the neural systems subserving face processing in neurotypically developing individuals.

CRediT authorship contribution statement

Emily K. Leiker: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Harma Meffert:** Data curation, Methodology. **Laura C. Thornton:** Writing - review & editing. **Brittany K. Taylor:** . **Joseph Aloi:** Writing - review & editing. **Heba Abdel-Rahim:** Data curation. **Niraj Shah:** Data curation. **Patrick M. Tyler:** Data curation. **Stuart F. White:** Writing - review & editing. **Karina S. Blair:** Methodology, Writing - review & editing. **Francesca Filbey:** Conceptualization, Writing - original draft, Writing - review & editing. **Kayla Pope:** Funding acquisition, Conceptualization. **Matthew Dobbertin:** Writing - review & editing. **R. James R. Blair:** Conceptualization, Funding acquisition, Project administration, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.09.004.

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